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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/079,241 | 02/20/2002 | Holly Hogrefe | 25436/2155 | 7186 |

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| EXAMINER |
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HUTSON, RICHARD G

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| ART UNIT | PAPER NUMBER |
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1652

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01/14/2008

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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|------------------------------|-------------------------------|--------------------------------|--|
| Office Action Summary | Application No. 10/079,241 | Applicant(s) HOGREFE ET AL. | |
| | Examiner Richard G. Hutson | Art Unit 1652 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/22/2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 64,65,70-82 and 85-97 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 64,65,70-82 and 85-97 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/5/2007 has been entered.

Applicant's cancellation of claims 24-27, 31-63, 83, 84, amendment of claims 64, 65, 70-81, 85, 86, 88-94, and the addition of new claims 95-97, in the paper of 7/5/2007 and 10/22/2007, is acknowledged. Claims 64, 65, 70-82, 85-97 are at issue and are present for examination.

Applicants' arguments filed on 7/5/2007 and 10/22/2007, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 86 and 89 are objected to because of the following informalities:

Claim 89 recites "0386" which should properly be "G386".

Newly amended claim 86 recites "YITDG SEQ ID NO:21)" which should be
"YITDG (SEQ ID NO:21)"

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64, 65, 70-82 and 85-97 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64, 65, 70-82 and 85-97 are indefinite in that they refer to an amino acid corresponding to Y410, T542, D543, K593, Y595, Y385, G387 and G388 of Pfu DNA polymerase and it is unclear what such an amino acid corresponding to is. The basis of this indefiniteness is two fold. First the recited amino acid positions are unclear with respect to "an amino acid position corresponding to" and second it is unclear what each of the recited positions refers to absent a specific amino acid sequence, such as a SEQ ID NO:

Claims 64, 65, 70-82 and 85-97 are further indefinite in that they each recite "reduced 5'-3' DNA polymerization activity" which is relative terminology and it is unclear what the reduced 5'-3' DNA polymerization activity is relative to.

Claim 65 is indefinite in that it recites "said DNA polymerase" of claim 64, however it is unclear which of the two different DNA polymerases of claim 64, that which has 5'-3' polymerization activity or that which is the second enzyme, to which claim 65 refers.

Claim 70 and 82 are indefinite in that they each refer to the enzyme mixture of claim 67 and claim 67 has been canceled.

Claim 74 is indefinite in that it recites said mutant JDF-3 DNA polymerase of claim 73 and there is no antecedent basis for such in claim 73.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64, 65, 70-82 and 85-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 64-94. In response to this rejection applicants cancelled claims 83, 84, amended claims 64, 65, 70-81, 85, 86, 88-94, and added new claims 95-97 and traverse the

rejection as it applies to the newly amended claims. Claims 95-97 are included in the rejection for the same reasons previously stated for claims 64-94.

Applicants continue to traverse the rejection on the following basis. Applicants submit that as amended, the claims recite a first enzyme comprising "5' - 3' polymerization activity of a DNA polymerase or reverse transcriptase", thus, clarifying that the activity possessed by the claimed enzyme is the DNA polymerization activity itself. Applicants submit that the specification teaches that all DNA polymerases possess 5' - 3' DNA polymerization activity and, further, specifically teaches over 30 examples of enzymes that possess the 5' - 3' DNA polymerization activity of a DNA polymerase or reverse transcriptase.

Based on the disclosure in the specification and state of the art at the time the instant application was filed, Applicants submit that they have demonstrated that they were in possession of the invention recited in the amended claims and, accordingly, request that the rejection be reconsidered and withdrawn.

Applicant's amendment and complete argument is acknowledged and has been carefully considered, however, is not found persuasive on the following basis. As amended applicants claims continue to be drawn to an enzyme mixture comprising a first and a second enzyme, wherein said first enzyme is any enzyme which comprises any 5'-3' polymerization activity of a DNA polymerase or reverse transcriptase and said second enzyme is a mutant DNA polymerase comprising a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388.

While applicants amendment of the recited mutant DNA polymerase to require certain structural domains is helpful in overcoming the rejection, it remains that applicants have not adequately described the referred to mutant DNA polymerases. Specifically with respect to the structure to function description of these mutants.

Further applicant's claims continue to be rejected on the basis that applicants have not adequately described the genus of those enzymes which comprise 5'-3' polymerization activity of a DNA polymerase or reverse transcriptase, beyond those enzymes which are a DNA polymerase or reverse transcriptase.

Given this lack of additional representative species of those enzymes beyond DNA polymerases and reverse transcriptases that have 5'-3' polymerization activity, as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 64, 65, 70-82 and 85-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme mixture comprising a DNA polymerase and a Reverse Transcriptase and a Pfu DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 19 with a

mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388, does not reasonably provide enablement for any enzyme mixture comprising first enzyme comprising a 5'-3' polymerization activity of a DNA polymerase or reverse transcriptase and a DNA polymerase comprising one or more mutations at positions Y410, T542, D543, K593, Y595, Y385, G387 and G388 of *Pfu* DNA polymerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 64-94. In response to this rejection applicants cancelled claims 83, 84, amended claims 64, 65, 70-81, 85, 86, 88-94, and added new claims 95-97 and traverse the rejection as it applies to the newly amended claims. Claims 95-97 are included in the rejection for the same reasons previously stated for claims 64-94.

Applicants continue to traverse the rejection on the following basis. Applicants submit that as noted above, Applicants have amended the claims to recite that the first enzyme has 5' - 3' activity of a DNA polymerase or reverse transcriptase. The instant specification teaches, and it is well known in the art that 5' - 3' polymerization activity is possessed by all DNA polymerases. Thus, between the teachings in the specification and the general knowledge in the art, Applicants have enabled numerous species of first enzymes having 5' - 3' DNA polymerization activity, such that one of skill in the art could readily practice the invention with respect to the first enzyme without having to engage in undue experimentation.

Applicants submit that with respect to the second enzyme, originally claimed as a mutant Archaeal DNA polymerase comprising selected mutations, the claims have been amended to delete reference to a mutant Archaeal DNA polymerase. Applicants submit that the claims recite that the second enzyme is a DNA polymerase comprising the partitioning domain sequence YXGG, the polymerase domain sequence DXXSLYP, the polymerase domain sequence YIDTDG, and the polymerase domain sequence KXY, and that the second enzyme has reduced 5' - 3' DNA polymerization activity and that the specification teaches that these partitioning and polymerase domain sequences are common to a number of Archaeal DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent (see page 27-29). Applicants submit that thus, the amended claims now place clear structural limitations on the claimed second enzyme, regardless of what mutations other than those specifically recited, may be encompassed by the use of the phrase "comprising an amino acid substitution".

Applicants submit that the claims recite, and the specification teaches, specific sites of mutation that result in a second enzyme that is able to catalyze the polymerization of deoxynucleotides, but that also has reduced 5' - 3' DNA polymerization activity and the specification provides specific guidance as to where mutations could be made in a DNA polymerase to reduce polymerization activity. Accordingly, the instant claims are enabled by the teachings of the specification and the general level of knowledge and skill in the art, and Applicants therefore request that the rejections be reconsidered and withdrawn.

Applicant's complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein.

Applicant's traversal that applicants have amended the claims to recite that the first enzyme has 5' - 3' activity of a DNA polymerase or reverse transcriptase is acknowledged, as well the fact that it is well known in the art that 5' - 3' polymerization activity is possessed by all DNA polymerases is acknowledged. This aspect of the claims remains insufficiently enabled on the basis that while it is recognized that all DNA polymerases have 5'-3' DNA polymerization activity, it remains what other enzymes also possess 5'-3' polymerization activity of a DNA polymerase or reverse transcriptase, but are not themselves DNA polymerases. Thus while applicants have enabled a subgenus of the claimed enzymes, such as DNA polymerase, applicants claims remain rejected for those enzymes which comprise 5'-3' polymerization activity of a DNA polymerase or reverse transcriptase.

Applicants traversal with respect to the second enzyme of the claimed mixture, that applicants have amended the claims to delete reference to a mutant Archaeal DNA polymerase and applicants have amended the claims to require that the second enzyme is a DNA polymerase comprising the partitioning domain sequence YXGG, the polymerase domain sequence DXXSLYP, the polymerase domain sequence YIDTDG, and the polymerase domain sequence KXY, and that the second enzyme has reduced 5' - 3' DNA polymerization activity and that the specification teaches that these partitioning and polymerase domain sequences are common to a number of Archaeal

DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent is also acknowledged. While this amendment is helpful in identifying those encompassed mutant DNA polymerases, the recited structural domains required by the mutant DNA polymerases remain insufficient to enable the full scope of those DNA polymerase mutants encompassed by the claims.

Because of this lack of sufficient guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the desired activities, it would require undue experimentation for one skilled in the art to arrive at the majority of those enzyme mixtures of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any enzyme mixture comprising an enzyme having any 5'-3' polymerization activity of a DNA polymerase or a reverse transcriptase and any mutant DNA polymerase with the specified motifs and specified mutations. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutant polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 64, 65, 70-82, 85-97 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9-14, 18, 20-22 and 36-51 of copending Application No. 10/035,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed enzyme mixtures of the instant application, comprising a first enzyme and a second enzyme wherein said first enzyme comprises a Archaeal DNA polymerase and said second enzyme is a mutant Archaeal DNA polymerase comprising a 3'-5' exonuclease activity and a reduced polymerization activity and having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon are anticipated by and thus obvious over the corresponding claims of copending Application No. 10/035,091, drawn to a enzyme mixture comprising a first enzyme and a second enzyme wherein said first enzyme comprises a DNA polymerization activity and

said second enzyme is a mutant Pfu DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant acknowledgment of this provisional rejection is acknowledged, as well as applicant's statement of their intent of filing a terminal disclaimer as a means of overcoming the rejection at the time at which the claims are found otherwise allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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A handwritten signature in black ink, appearing to read 'Richard G. Hutson', followed by a long horizontal line extending to the right.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

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1/6/2008